

Establishment of Human Trophoblast Progenitor Cell Lines from the Chorion.

Journal:	Stem Cells
Publication Year:	2011
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PubMed link:	21755573
Funding Grants:	Constructing a fate map of the human embryo, SFSU Bridges to Stem Cell Research

Public Summary:

The placenta is a transient organ that attaches the baby to the mother's uterus. This connection is severed at the time of delivery and the placenta's nine-month lifespan is over. This organ plays many critical roles during pregnancy. Its specialized cells, termed trophoblasts, invade the uterine wall using mechanisms that are similar to cancer cells. This process diverts maternal blood flow to the placenta, which regulates the passage of substances, including nutrients and oxygen, to the baby. Thus, it is not surprising that placental malfunctions are associated with many pregnancy complications. Finally, the placenta, like the baby, carries a nearly equal complement of genes from the mother and the father. In other settings (example, kidney transplantation) this incompatibility leads to organ rejection. Somehow placental cells have learned how to avoid this fate. Despite these interesting features and essential functions, relatively little is known about how the placenta develops. Trophoblast stem cells that differentiate into the mature trophoblast subtypes have been isolated in many species. In humans, we lack these cell-based tools. Accordingly, we carried out a systematic search to locate these cells within the placenta and used this information to devise a procedure for isolating them. To locate the cells, we used a strategy that stem cell scientist have successfully employed to identify progenitors in other organs and tissues. Specifically, we looked for cells that co-expressed general markers of the undifferentiated state and master regulators that govern initial steps in trophoblast differentiation. We found these cells deep within the placenta. Knowing their location allowed us to design a dissociation procedure for enriching this population. The next problem to solve was how to get them to grow in an undifferentiated state in the laboratory. From the published work of other scientists we narrowed down the list of molecules that we thought might be involved and added them to the culture medium, the liquid food in which cells are grown. These experiments produced interesting results. Stable lines of cells emerged that grew continuously in the laboratory in an undifferentiated state as determined by the expression of the sets of markers that we originally used to identify this population in intact placentas. Next we asked whether these cells could differentiate into the trophoblast subtypes. To answer, we switched the cells to media formulations that we know from our earlier work triggers these processes. Indeed we were able to produce tumor-like invasive trophoblasts that had the unique molecular fingerprint of these very unusual cells. We used a different medium to promote differentiation of the trophoblast population that transports substances to/from the baby. These cells also have unique characteristics. For example, they fuse with one another and secrete hormones that are specific to the placenta, including human chorionic gonadotropin, the detection of which is the basis of all pregnancy tests. Thus, we isolated human trophoblast progenitors, important new tools that we and other scientists can use to study the critical early stages of placentation in our own species.

Scientific Abstract:

Placental trophoblasts are key determinants of in utero development. Mouse trophoblast stem cells (mTSCs), which were first derived over a decade ago, are a powerful cell culture model for studying their self-renewal or differentiation. Our attempts to isolate an equivalent population from the trophoblast of human blastocysts generated colonies that quickly differentiated in vitro. This finding suggested that the human placenta has another progenitor niche. Here we show that the chorion is one such site. Initially, we immunolocalized pluripotency factors and trophoblast fate determinants in the early-gestation placenta, amnion and chorion. Immunoreactive cells were numerous in the chorion. We isolated these cells and plated them in medium containing FGF and an inhibitor of activin/nodal signaling, which is required for human embryonic SC self-renewal. Colonies of polarized cells with a limited lifespan emerged. Trypsin dissociation yielded continuously self-replicating monolayers. Colonies and monolayers formed the two major human trophoblast lineages-multinucleate syncytiotrophoblasts and invasive cytotrophoblasts (CTBs). Transcriptional profiling experiments revealed the factors associated with the self-renewal or differentiation of human chorionic trophoblast progenitor cells (TBPCs). They included imprinted genes, NR2F1/2, HMGA2 and adhesion molecules that were required for TBPC differentiation. Together, the results of

these experiments suggested that the chorion is one source of epithelial CTB progenitors. These findings explain why CTBs of fully formed chorionic villi have a modest mitotic index and identify the chorionic mesoderm as a niche for TBPCs that support placental growth.

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